IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Atty Dkt. 2801-18
C# M#

BOTTAZZI et al. TC/A.U. 1644

Serial No. 09/555,473 Examiner: NOLAN

Filed: February 26, 2002 Date: May 13, 2004

Title: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SUPPLEMENTAL SUBMISSION

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $ 86.00	$	0.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	0.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**0.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☐ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	0.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Other:		**0.00**
TOTAL FEE ENCLOSED	$	**0.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: _____

JFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOTTAZZI et al. Atty. Ref.: 2801-18; Confirmation No. 9420

Appl. No. 09/555,473 TC/A.U. 1644

Filed: February 26, 2002 Examiner: NOLAN

For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

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May 13, 2004

Commissioner for Patents
P.O. Box 1450
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Sir:

SUPPLEMENTAL SUBMISSION

Supplemental to the Information Disclosure Statement filed March 16, 2004, the Request filed March 16, 2004, the Response filed March 16, 2004 and the Declaration of Rita De Santis executed January 8, 2004, which was submitted with the Response dated January 16, 2004, consideration of the following as well as the attached is also requested.

The Examiner has asserted the following:

> Claims 17-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alles et al., [Blood, Vol. 84, No. 10 (November 15) 1994, pp 3483-3493] of record, as evidenced by ATCC catalog number 30-2002. On page 3485, 1st full paragraph, the Alles et al., reference **teaches** expressing the full length human **PTX3 protein in COS cells and incubated in DMEM and then isolating the protein in the supernatant** for Western

> analyses. **At the point the protein was isolated in the supernatant that had DMEM in it**, the claims drawn to a pharmaceutical composition were anticipated. As evidenced by the ATCC Catalog No. 30-2002, **Dulbecco's Modified Eagle's Medium, Modified Formulation, is useful as an in vivo solution, thereby meeting the pharmaceutical composition limitation** (see, Office Action dated May 1, 2003, emphasis added).

The applicants have previously submitted evidence, in the form of a Declaration of Rita De Santis executed January 8, 2004, that one of ordinary skill in the art would believe the cited Alles et al. reference does not teach pharmaceutical compositions or pharmaceutical compositions containing an active ingredient of the claimed invention. One basis for the Declarant's view was that the DMEM culture media of the Alles et al. composition was not a pharmaceutically acceptable excipient, as required by the present claims. Another basis for the Declarant's view, as expressed in the Declaration, was the belief that one of ordinary skill will appreciate that Alles et al. does not provide a pharmaceutical composition and/or pharmaceutically acceptable excipient because, for example, the supernatant of Alles et al described on page 3485, first full paragraph of Alles et al., for example, would not be expected to be an administerable pharmaceutical composition. More specifically, the Declarant explained that she believed that one of ordinary skill in the art will appreciate that it is more likely than not that the solution of Alles et al. contain, for example, COS cell metabolites, catabolites and residual components of the cellular lysis, such as virus related to or released by the DNA of the COS cells.

The Examiner responded by stating that because the claims are open to include "other constituents" and because DMEM "is used to keep living cells alive, it is art

recognized not to be detrimental to living tissues and therefore a composition of the pentraxin protein in DMEM would constitute a pharmaceutical composition," see, Advisory Action dated February 20, 2004.

The applicants respectfully submit that the Examiner has focused on the constituents of DMEM, as opposed to the composition of the cited art, in comparison with the claimed invention. Specifically, the Examiner initially characterized Alles et al. as teaching PTX3 in a COS cell supernatant containing DMEM. The composition of Alles et al. therefore contains more than DMEM and PTX3.

For reasons further detailed below, the applicants believe that even a solution of DMEM and PTX3 would not anticipate the presently claimed invention.

Initially however, the cited art teaches, at best a COS cell supernatant in a cell culture media and a protein. Moreover, the pending claims require an administerable pharmaceutical composition. The composition of Alles et al. is not an administerable pharmaceutical composition, as presently claimed.

Consideration of the following discussion, and attached copy of the Federal Register, are requested, in support of the Declarant's previous characterization of how one of ordinary skill in the art would interpret Alles et al.

The attached copy of FR Vol. 63, No. 110, Tuesday, June 9, 1998, pages 31506-31513, provides the U.S. FDA Draft Guidance on Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. The attached FDA Draft was published between the filing of the applicants' priority application and the International Application PCT/IT98/00364. The attached FDA Draft is further evidence of how one of ordinary skill in the art would view administerable proteins and polypeptides, their

derivatives, and products of which they are components. (See, 63 FR 31508, § 1.2 Scope, ¶1), such as the alleged products of Alles et al.

Specifically, for example, § 2.0 of the attached Draft Guidance provides a number of General Principles for Consideration in Setting Specifications, which includes the following with regard to impurities and contaminants.

> • Impurities
> In addition to evaluating the purity of the drug substance/drug product, ... **the manufacturer should also assess impurities which may be present.** Impurities may be either process- or product-related.
> ...
> **Process-related impurities encompass those that are derived from** the manufacturing process, i.e. derived from **the culture (e.g., inducers, antibiotics, or media components)** or from downstream processing (see appendix section 6.2.1)...
> • Contaminants
> Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, Such as chemical/biochemical materials (e.g., microbial proteases) and/or microbial species. Contaminants should be strictly avoided and/or suitably controlled...
> **Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" should be considered.** (63 FR 31509, emphasis added).

On page 31510, § 4.1.3 further details issues relating to purity and impurity as follows:

> ...Since the absolute purity of biotechnological/biological products is difficult to determine and the results are method-dependent (section 2.1.4), the purity of the drug substance is usually estimated by a combination of methods. The impurities observed in these products are classified as process-related and...
> • **Process-related impurities** (section 2.1.4) in the drug substance may include **culture media, host cell proteins, DNA,** monoclonal antibodies and chromatographic media used in purification, solvents/buffer components. **These impurities should be minimized by the use of**

> **appropriate well-controlled manufacturing processes**...". (emphasis added).

On page 31511, § 5.0, in the Glossary, the Draft Guidance defines "impurity" as follows:

> **Impurity**:
> **Any component present in the drug substance or drug product that is not the desired Product**, a product-related substance, or an excipient (including added buffer components). It may be either process- or product-related. (emphasis added).

With specific regard to **Process-related impurities**, the Draft states as follows:

> Process-related impurities:
> Impurities that are derived from the manufacturing process. They may be **derived from cells substrates, culture (e.g., inducers, antibiotics, or media components),** or from downstream processing (e.g., processing reagents or column leachables). (emphasis added).

Moreover, § 6.2.1, on page 31512, of the attached Draft describes **Process-related impurities** as follows:

> These are derived from the manufacturing process (section 2.1.4) and are classified into three major categories: Cell substrate-derived, culture-derived, and downstream-derived.
> (a) **Cell substrate-derived impurities include proteins/polypeptides derived from the host organism; nucleic acid (host cells generic/vector/total DNA); polysaccharides; viruses**. ... The **level of DNA from host cells can be detected by direct analyses on the product** (such as hybridization techniques) and/or by spiking experiments (laboratory scale) **demonstrating the removal of nucleic acid by the purification process**. For intentionally introduced viruses, the ability of the manufacturing process to remove/inactivate viruses should be demonstrated as described in the ICH guidance Q5A "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. (emphasis added).

The above and attached are submitted as further evidence that one of ordinary skill in the art would not consider the solution indicated by the Examiner in Alles et al. as an administerable pharmaceutical composition, as required by the present claims.

That is, even if DMEM is an excipient, as required by the claims, which the applicants do not believe it is, the solution of Alles et al. relied upon by the Examiner is not an administerable pharmaceutical composition of the claims. Alles et al. fail to teach or provide each aspect of the presently claimed invention.

Specifically, one of ordinary skill in the art will appreciate that the solution of Alles et al. noted by the Examiner, will contain **inducers**, **antibiotics**, or **media components** which the attached Federal Register document indicates are impurities, which should not be present in administerable pharmaceutical compositions.

Moreover, § 4.1.3 of the attached states that **Culture media (i.e. DMEM)**, **host cell proteins (such as CHO cells) and DNA (such as from CHO cells)** which are more likely than not contained in the Alles et al. composition, are considered Process-related impurities which should not be present in administerable pharmaceutical compositions, such as the claimed invention.

In view of the above and attached, the applicants submit that the claims are patentable over the art of record and a Notice of Allowance is requested.

The Examiner is again requested to contact the undersigned if anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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